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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/091,360

03/04/2002

Petros Tsipouras

IK-110.3(C)

1541

47670

7590

11/28/2008

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EXAMINER

CLOW, LORI A

ART UNIT

PAPER NUMBER

1631

MAIL DATE

DELIVERY MODE

11/28/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/091,360	Applicant(s) TSIPOURAS ET AL.	
	Examiner Lori A. Clow	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 November 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 40,41,45 and 47-55 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 40,41,45 and 47-55 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/3/2008</u> | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1631

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3 November 2008 has been entered.

Applicants' response, filed 3 November 2008, has been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 40, 41, 45, and 47-55 are currently pending. Claims 1-39, 42-44, and 46 have been cancelled.

Information Disclosure Statement

The Information Disclosure Statement filed 3 November 2008 has been considered. A signed copy of PTO form 1449 is included with this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 40, 41, 45, and 47-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,169,816 (Ravkin; previously cited), in view of US 2004/0072364 (Tisone et al.; previously cited), in further view of US 5,287,272 (Rutenberg et al.). This rejection is newly applied and is necessitated by claim amendment.

The instant claims are drawn to a method for rare cell bright field and bright field microscopic image detection and identification.

Ravkin teaches computer implemented imaging, using a combination of brightfield and fluorescence images of smears of fetal nucleated red blood cells (NRBCs) and other objects, such as red blood cells (RBCs) and white blood cells (WBCs) (abstract, column 11 lines 65-67 to column 2, line 1). The objects in the sample are stained with a fluorescent dye that selectively stains nuclei and a dye that selectively stains fetal hemoglobin in the cytoplasm of fetal NRBCs. These include two different illumination schemes, such that candidate regions of interest (blobs) are identified for further processing (column 1, lines 65-67 to column 2, lines 1-20). The invention is directed to an evaluation that includes enrichment of fetal NRBCs from maternal blood, positive identification of fetal NBRCs (signal one), and genetic analysis (signal two) (column 3, lines 30-33).

Art Unit: 1631

In regard to claims 47, steps (i) and (ii) and claim 48, Ravkin teaches that a set of features that identify fetal NRBCs are created to distinguish them from other types of cells. This is done by creating contrast in cells containing fetal hemoglobin and another type of contrast in cells having a nucleus. The slide is reacted with a reagent (antibody) to produce a signal (column 3, line 58-667 to column 4, lines 1-6). The images are processed (digitized; column 4, line 53) to provide derivative images that are correlated to a region of interest. From there further analysis of only the region of interest is performed, such that the image falls into a specific class of object (column 7, lines 44-57). Ravkin teaches that the invention is carried out to identify objects for further analysis such as FISH. A FISH sample is prepared using probe that binds to a particular DNA sequence in the chromosomes in the sample and the probe is labeled. Slides are laid out with coordinates of reference points (column 4, lines 8-11). The system also comprises motor and lamp controllers (column 5, lines 11-25).

In regard to claim 48, Ravkin further teaches that the microscopic system is computerized (column 5, line 66-67 to column 7, lines 1-5). Further, the computer system comprises processors that are linked with any number of peripheral devices (column 6, lines 1-7).

In regard to claim 40, Ravkin teaches large field sample images (column 7, sections 5 and 6)

Ravkin teaches varying concentrations of rare cells as in claim 41 at column 3, lines 41-45.

In regard to claim 45, Ravkin teaches a computer readable storage medium for the system (column 6, lines 59-67).

Art Unit: 1631

Ravkin does not specifically teach the embodiments of claim 47, step (iii) and claim 48 that are drawn to the computer-controlled dispensing system to apply the label or tag to the candidate image. However, Tisone et al. teach a dispensing apparatus and method for dispensing reagent onto a substrate in which the dispensing apparatus has a dispensing head that is responsive to a first signal to dispense droplets of reagent onto a substrate. The substrate or dispensing head are secured in association with a table or carriage. The table is responsive to a second signal for providing for relative X, X-Y or X-Y-Z motion. The controller is adapted to receive data representative of a desired reagent pattern and to output and coordinate the first and second signals so as to cause relative motion between the substrate and the dispensing head and to cause the dispensing head to dispense droplets of reagent at one or more desired locations (abstract). Tisone teach that the apparatus may be used for dispensing onto a glass slide (page 3, column 2, paragraph [0038]. In regard to claims 50, 51, and 53 the system moves in respect to the signals received and there are a series of stepper motors to move the platform, the dispensing head or carriage (page 4, column 4, paragraph [0048]. Tisone teaches that the system comprises displacement pumps for dispensing reagent (page 4, column 2, paragraph [0049] (as in claim 54).

Neither Ravkin nor Tisone specifically teach that the sample slide is transported from a storage module on to a microscope stage and visa versa, as is presently claimed. However, Rutenberg teaches an automated screening system and method for cytological specimen classification in which the automated microscope system includes a robotic slide handler which upon appropriate commands from the computer system moves the specimen slides from a cassette holder to a motorized movable stage for transport into and within the optical path of the microscope (column 5, lines 1-9).

Art Unit: 1631

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have incorporated the reagent dispensing methods of Tisone with the computerized microscope elements of Rutenberg and the rare cell detection system and methods of Ravkin, as Ravkin teaches that techniques for interfacing the computer to external instruments are known and the system may be in communication with a number of peripheral devices via a bus subsystem (column 6, lines 1-10). Further, Tisone motivates one to combine such methods, as well, as Tisone teaches that a host computer is the central controller (paragraph 0063) and that various configurations exist for the system (paragraph 0118 and 0119). One of ordinary skill in the art of computers could have clearly configured both such that the systems, when combined, meet the limitations of the instant claims. One of skill in the art would have had a reasonable expectation of success in programming a computer to control various aspects of the microscope functions, as are taught by Ravkin, Tisone and Rutenberg.

Ravkin, Tisone, and Rutenberg do not teach the specific limitations of dispensing a label as the reagent, as in claim 48. However, it would have been obvious to one of skill in the art to dispense a label as the reagent, as the system of Ravkin is clearly for use with fluorescent techniques (FISH).

Claims 48 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,169,816 (Ravkin; previously cited), in view of US 2004/0072364 (Tisone et al.; previously cited), in further view of US 5,287,272 (Rutenberg et al.), as applied to claim 48 above, in further view of US 5,681,741 (Atwood et al.).

Art Unit: 1631

Ravkin teaches computer implemented imaging, using a combination of brightfield and fluorescence images of smears of fetal nucleated red blood cells (NRBCs) and other objects, such as red blood cells (RBCs) and white blood cells (WBCs) (abstract, column 11 lines 65-67 to column 2, line 1). The objects in the sample are stained with a fluorescent dye that selectively stains nuclei and a dye that selectively stains fetal hemoglobin in the cytoplasm of fetal NRBCs. These include two different illumination schemes, such that candidate regions of interest (blobs) are identified for further processing (column 1, lines 65-67 to column 2, lines 1-20). The invention is directed to an evaluation that includes enrichment of fetal NRBCs from maternal blood, positive identification of fetal NRBCs (signal one), and genetic analysis (signal two) (column 3, lines 30-33).

Ravkin teaches that a set of features that identify fetal NRBCs are created to distinguish them from other types of cells. This is done by creating contrast in cells containing fetal hemoglobin and another type of contrast in cells having a nucleus. The slide is reacted with a reagent (antibody) to produce a signal (column 3, line 58-667 to column 4, lines 1-6). The images are processed (digitized; column 4, line 53) to provide derivative images that are correlated to a region of interest. From there further analysis of only the region of interest is performed, such that the image falls into a specific class of object (column 7, lines 44-57). Ravkin teaches that the invention is carried out to identify objects for further analysis such as FISH. A FISH sample is prepared using probe that binds to a particular DNA sequence in the chromosomes in the sample and the probe is labeled. Slides are laid out with coordinates of reference points (column 4, lines 8-11). The system also comprises motor and lamp controllers (column 5, lines 11-25).

Art Unit: 1631

Ravkin further teaches that the microscopic system is computerized (column 5, line 66-67 to column 7, lines 1-5). Further, the computer system comprises processors that are linked with any number of peripheral devices (column 6, lines 1-7).

Ravkin, Tisone, and Rutenberg do not specifically teach that the slide is moved to a thermocycling station. However, Atwood teaches an *in situ* PCR system for nucleic acids contained in a prepared cell or tissue sample in which samples are contained on a slide (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have configured the system of Ravkin, Tisone, and Rutenberg with the ability to move a slide to a thermocycling station for *in situ* PCR, as taught by Atwood. Atwood teaches that the handling of the microscope slide for assembly can be automated (column 12) as can the hotstart application (column 14), thus giving one of ordinary skill in the art expectation of success to incorporate such an element into the automated microscope systems of Ravkin, Tisone, and Rutenberg for greater capabilities of the system to identify a rare cell.

Response to Applicant's Arguments

1. Applicant argues with regard to Ravkin that “there is no disclosure of the claimed automatic placement of the slide on the stage and the removal of the slide from the stage to or from a storage module or the automatic placement of the slide onto another device on the stage, such as a thermally cycling device.

Applicant's arguments with respect to the above have been considered but are moot in view of the new ground(s) of rejection that includes the automated slide removal and storage of Rutenberg.

Art Unit: 1631

2. Applicant argues that the “cited system is computerized only with respect to image analysis, but not automated with respect to placement, removal, or storage of the slide or even of the slide to a peripheral device on or off the stage”.

Applicant's arguments with respect to the above have been considered but are moot in view of the new ground(s) of rejection that includes the automated slide removal and storage of Rutenberg.

3. Applicant argues that “neither the Ravkin reference nor the Tisone reference disclose nor suggest a means to move the slide automatically to a thermocycler or similar instrument”.

Applicant's arguments with respect to the above have been considered but are moot in view of the new ground(s) of rejection that includes the automated slide removal and storage of Rutenberg and the in situ PCR of Atwood.

4. Applicant argues that "the reading of the disclosure [of Tisone] is incorrect because it is not even remotely relevant". Applicant states that "Tisone in paragraph [0118] discloses...EPROMS could connect to one or more microprocessors...to provide signal to each electromechanical device but then in the next paragraph [0119] only writes of various liquids and liquid handling permutations whilst remaining silent on adapting features outside of liquid handling".

This is not persuasive. As noted above it is Ravkin who teaches that techniques for interfacing the computer to external instruments are known and the system may be in communication with a number of peripheral devices via a bus subsystem (column 6, lines 1-10). Certainly, one of skill in the art of computer sciences would have reasonable expectation of success in combining the two systems, as they both teach host computers with central controllers

Art Unit: 1631

and contemplate various configurations for such systems. Further, Ravkin specifically teaches interfacing a computer to external instruments (column 5, lines 22-25). The computer system of Ravkin is used not only to control motion, but also to perform image acquisition and processing and user interface functions (column 5, line 66 to column 6, line 1). A bus subsystem is used such that not all components need be located in a single space. Finally Ravkin teaches using this system for further analysis, such as FISH, in which fluorescent labels are applied, leading one of skill in the art to a reasonable expectation of success in combining a reagent dispensing system to the automated microscope system for streamline analysis.

Conclusion

No claims are allowed.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of

Art Unit: 1631

the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

November 27, 2008

/Lori A. Clow/

Primary Examiner, Art Unit 1631